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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/725,013	12/02/2003	Lakshman R. Sehgal	3840-005-27	3180

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DLA PIPER RUDNICK GRAY CARY US LLP
ATTN: PATENT GROUP
1200 NINETEENTH STREET, NW
WASHINGTON, DC 20036

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/725,013	SEHGAL ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-33* is/are pending in the application.

4a) Of the above claim(s) *14-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-13,28-33* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Final Rejection

Claims 1, 2, and 4-33 are pending.

Applicant's traversal, the amendment to the specification, the cancellation of claim 3, the amendment to claims 1 and 6, and the addition of claim 33 in paper filed on 5/5/06 is acknowledged and considered.

Election/Restrictions

This application contains claims 14-27 drawn to an invention nonelected and Perfluorochemical emulsion in claim 10 and sodium bicarbonate and antibiotic-antimycotic in claims 12 and 28 drawn to species nonelected with traverse in Paper No. 11/30/05. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, and 8 remain rejected and claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over French et al. (US 6,290,949) taken with Kochanek et al. (US 5981225). French teaches an ex vivo method of gene therapy for treating a vascular disease in a mammal (preferably human), comprising treating a graft (veins or arteries) with a gene transfer vector (replication defective adenoviral vector) comprising a nucleic acid operably linked to a promoter. See columns 13-18. The nucleic acid can encode TM. See column 5. French teaches that either the RSV promoter or the CMV promoter can be used in the replication defective adenoviral vector. See column 7. However, French does not specifically teach using a gutless adenoviral vector in the method.

However, at the time the invention was made, one of ordinary skill in the art understood that gutless adenoviral vectors contain a minimal amount of adenovirus DNA and are incapable of expressing any adenovirus antigens. In addition, gutless adenovirus vectors provide

significant advantage over first and second-generation adenoviral vectors because they can accommodate large inserts of foreign DNA while completely elimination the problem of expressing adenoviral genes that result in immunological response to viral proteins. See Kochanek et al. (columns 2-3). The instant specification teaches that, at the time of filing, several methods for producing gutless adenoviral vectors were known to one of ordinary skill in the art. See pages 17 and 24.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of French taken with Kochanek, namely to use a gutless adenoviral vector in the method. One of ordinary skill in the art would have been motivated to combine the teaching because gutless adenoviral vector eliminate the problem of expressing adenoviral genes that result in an immunological response to adenoviral proteins.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of French taken with Kochanek, namely to use the method to treat a human. One of ordinary skill in the art would have been motivated to combine the teaching to treat a human having a vascular disease because TM is well known to one of ordinary skill in the art for treating vascular disease in a subject.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 5/5/06 have been fully considered but they are not persuasive.

In response to applicant's argument that the examiner is applying an improper "obvious to try" rationale in supporting an obviousness rejection, the argument is not found persuasive

because the examiner has set forth motivation for using gutless adenoviral vectors comprising a nucleic acid encoding TM in an ex vivo method of gene therapy for treating a vascular disease. The applicant has not addressed these reasons for combining the references in their arguments.

In response to applicant's argument that the examiner fails to address whether there is reasonable expectation of success as required by MPEP 2143.02, the argument is not found persuasive because when the reference(s) relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). There is no evidence of record to rebut the presumption of operability.

In response to applicant's argument that the infection and expressing conditions would need to be reestablished through an enormous experimentation, the argument is not found persuasive because the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). This is the case here. The applicant indicates that, at the time the invention was made, one of ordinary skill in the art typically engages in such experimentation. See pages 17 and 24 of the instant specification.

In response to applicant's argument that the present invention provides an unexpectedly superior effect for the clinic application for treating thrombic vascular diseases, the argument is not found persuasive because other than applicant's assertion of the unexpectedly superior effect

for clinic application for treating thrombic vascular diseases, there is not evidence of record to support applicant's assertion. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). In addition, the applicant contemplates practicing the claimed invention and do not actually practice the claimed invention.

The Declaration under 37 CFR 1.132 filed 5/5/06 is insufficient to overcome the rejection of claims 1,3,4, and 8 based upon 103(a) as set forth in the last Office action because: of the reasons set forth above. Several statements made in the Declaration have already been addressed above in response to applicant's arguments.

Applicant argues that it is known in the art that certain proteins can interfere with adenovirus production. See Kagawa et al. (Gene Therapy 7:75-79, 2000), teaching that apoptotic gene Bax results in premature death of the 293 packaging cell line resulting in minimal yields of the recombinant virus.

Applicant's argument is not found persuasive because the apoptotic gene Bax is structurally and functionally different than a gene encoding TM. Expressing of TM does not result in apoptosis of a cell. There is no evidence of record that expressing TM in packaging cells results in premature cell death of packaging cells. When the reference relied on expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide facts rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980).

With respect to applicant's argument that the claimed method is different with respect to the step of "grafting the virus-treated blood vessel in said mammal, wherein said thrombomodulin protein or its variant is expressed in said virus-treated blood vessel in an amount sufficient to reduce re-occlusion and/or intimal hyperplasia in the grafted blood vessel", the argument is not found persuasive because the material and method step(s) recited in the French taken with Kochanek are the same material and method step(s) recited in the claimed method. See In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). There is nothing in the recited method steps or material used that differentiates the claimed invention from the method taught in the prior art. See In re King, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986).

Claims 1 and 5 remain rejected under 35 U.S.C. 103(a) as being unpatentable over French taken with Kochanek as applied to claims 1, 4, and 8 above, and further in view of Salyapongse et al. (AL).

French taken with Kochanek do not specifically teach using an inducible system to control expression of the polynucleotide encoding TM.

However, at the time the invention was made, regulating transgene expression using inducible promoters was well known to one of ordinary skill in the art as exemplified by Salyapongse et al. (page 668). Salyapongse teaches that using an inducible promoter helps overcome the problem of controlling transgene expression using constitutive promoters (page 668).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of French taken with Kochanek in further view

of Salyapongse, namely to use an inducible system to express the TM protein. One of ordinary skill in the art would have been motivated to combine the teaching because an inducible can be used to regulate the expression of the protein in the blood vessel.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 5/5/06 have been fully considered but they are not persuasive for the reasons set forth above in the previous 103(a) rejection.

Claims 1, 6, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over French taken with Kochanek as applied to claims 1, 4, and 8 above, and further in view of He et al. (PNAS, 95: 2509-2514).

French taken with Kochanek do not specifically teach using a shuttle vector with the structural limitations as recited instant claim 6 to produce the gutless adenoviral vector.

However, at the time the invention was made, the shuttle vector described in instant claim 6 was known to one of ordinary skill in the art as pAdEasy that can be ordered from Stratagene (page 24 of the instant specification). He et al. teaches that pAdEasy is a simplified system for generating adenoviruses (pages 2509-2510). He teaches that pAdEasy contains a kanamycin resistance gene (page 2510).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of French taken with Kochanek in further of He, namely to produce the gutless adenoviral using the claimed shuttle vector and use the gutless vector in the method. One of ordinary skill in the art would have been motivated to combine the

teaching and use pAdEasy for producing the gutless adenoviral vector because pAdEasy is a simplified system for generating recombinant adenoviruses as exemplified by He (page 2509).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 5/5/06 have been fully considered but they are not persuasive for the reasons set forth above in the previous 103(a) rejections.

Claims 1, 9-13, and 28-32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over French taken with Kochanek as applied to claims 1, 4, and 8 above, and further in view of Sehgal et al. (4,826,811) and Kibbe et al. (J. Vasc. Surg. 34: 156-65, 2001).

French taken with Kochanek do not specifically teach the method step recited in instant claims 9 and 28.

However, at the time the invention was made, an acellular oxygen carrier (unmodified hemoglobin or chemically modified hemoglobin) was well known to one of ordinary skill in the art for preserving a graft as exemplified by Sehgal et al. See column 4. In addition, the concentration for hemoglobin was well known to one of ordinary skill in the art as exemplified by Sehgal et al. See column 16.

In addition, at the time the invention was made, using a 1:1 mixture of Ham's F12 medium and DMEM for culturing a blood vessel (vein) in vitro transfected with a replication defective adenovirus was well known to one of ordinary skill in the art for as exemplified by Kibbe et al. See page 157. In addition, L-glutamine is used in the mixture. See page 157.

Kibbe further teaches transfecting the vein with an E1 and E3 defective adenovirus and incubating the vein for 30 minutes. See page 157.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of French taken with Kochanek in further view of Sehgal and Kibbe, namely to the method steps as recited in instant claim 9, 28, and 29. One of ordinary skill in the art would have been motivated to combine the teaching because unmodified and chemically modified hemoglobin are used for preserving a graft. In addition, one of ordinary skill in the art would have been motivated to combine the teaching because a 1:1 mixture of Ham's F12 medium and DMEM was well known to one of ordinary skill in the art for culturing cells in vitro. Furthermore, one of ordinary skill in the art would have been motivated to incubate the blood vessel with the complex delivery system for a desired period of time (30 minutes) to assure sufficient transfection of the blood vessel with the gutless adenoviral viral vectors as exemplified by Kibbe (page 157).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of French taken with Kochanek in further view of Sehgal and, namely to the use unmodified hemoglobin in the range of 3 g/dl to 10 g/dl in the method. One of ordinary skill in the art would have been motivated to combine the teaching because the range was readily available to one of ordinary skill in the art for preserving a graft. See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 5/5/06 have been fully considered but they are not persuasive for the reasons set forth above in the previous 103(a) rejections.

In response to applicant's argument that the disclosed preservative medium is critical for success of the medical application, the argument is not found persuasive because several of the claims do not recite using the medium. Furthermore, the medium was well known in the art at the time the invention was made. In addition, if the medium is critical for success for practicing the claimed invention, then there could be a potential rejection under 112 first paragraph enablement for practicing the full scope of the claimed method.

Double Patenting

Applicant is advised that should claim 12 be found allowable, claim 28 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Response to Arguments

Applicant's arguments, see pages 8-9, filed 5/5/06, with respect to 112 first paragraph have been fully considered and are persuasive. The rejection of claims 1, 2, 6-13, and 28-32 has been withdrawn because of the amendment to claim 1.

Applicant's arguments, see page 9, filed 5/5/06, with respect to 112 second paragraph have been fully considered and are persuasive. The rejection of claims 3 and 4 has been withdrawn because of the amendment to claim 4 and the cancellation of claim 3.

Conclusion

Claims 1, 2, and 8 would be provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 24-26 and 28-29 of copending Application No. 10/785,156. However, the claims of '156 are drawn to a non-elected invention.

Claim 2 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, SPE – Art Unit 1635, can be reached at (571) 272-4517.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman

RICHARD SCHNIZER, PH.D.
PRIMARY EXAMINER